High throughput modeling of human neurodegenerative diseases in embryonic stem cells

Grant Award Details

High throughput modeling of human neurodegenerative diseases in embryonic stem cells

Grant Type: New Faculty II

Grant Number: RN2-00919

Project Objective: The goal of this project is to use floxin technology, which was developed by the PI to allow facile introduction of modified alleles at trapped loci in the genome of mouse ESC, to introduce tagged human disease alleles at loci implicated in human neuronopathies. The engineered alleles include constructs that facilitate subcellular localization and protein purification of the gene under study. The engineered mESC lines will then be used to study disease phenotypes.

Investigator:

Name:	Jeremy Reiter
Institution:	University of California, San Francisco
Type:	PI

Disease Focus: Amyotrophic Lateral Sclerosis, Neurological Disorders, Neuropathy

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $2,259,092

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Grant Application Details

Application Title: High throughput modeling of human neurodegenerative diseases in embryonic stem cells

Public Abstract: An important class of neurological diseases predominantly affects spinal motor neurons, the neurons that control muscle movement. The most well known of these motor neuronopathies is Amyotrophic Lateral Sclerosis (ALS), commonly referred to as Lou Gehrig's disease for the famous Yankee first baseman who died of the disease. The first symptoms of ALS are usually increasing difficulty walking or speaking clearly. People with ALS progressively lose their ability to initate and control movements, and may become totally paralyzed during the late stages of the disease. There are no cures or effective treatments for these diseases. Riluzole (Rilutek), the only FDA approved medication for ALS, only modestly slows disease progression. Consequently, ALS is usually fatal within one to five years from onset, with half dying within eighteen months. Although genetic studies have identified many mutations that cause these diseases, it is not understood why these mutations kill motor neurons. This lack of understanding about the root causes of motor neuron diseases currently hinders the development of effective treatments. We seek to study motor neurons carrying these mutations in cell culture dishes to understand how these diseases sicken and kill these cells. To generate these motor neurons, we will use embryonic stem cells. Embryonic stem cells can become any cell in our body, including motor neurons. We have developed a new technology that allows us to quickly replace healthy genes with mutant genes in mouse embryonic stem cells. We will use this technology to insert both normal and disease-associated versions of genes into embryonic stem cells. Study of the healthy and mutant mutant motor neurons derived from these embryonic stem cells will shed light on the ways in which the mutations cause harm. The development of cell based models of human diseases is likely to have additional benefits as well. For example, diseased motor neurons grown in cell culture dishes can be quickly and efficiently screened with potential drugs to discover agents that slow, halt or reverse the cellular damage. It is our hope that these experiments will both deepen our understanding of important neurodegenerative disorders, and lead to new directions for the development of effective therapies.

Statement of Benefit to California:	Over 6,000 Americans are diagnosed each year with motor neuronopathies, about the same as are diagnosed with multiple sclerosis. One form of this illness, ALS, is responsible for about one in every 800 deaths, and cause many lengthy and costly hospital admissions. We propose using stem cells to model these diseases so that we can gain a deeper understanding of their root causes. It is our expectation that this deeper understanding will lead to new and better approaches to the treatment of these disorders. In addition, our technology for developing embryonic stem cell-based models of human diseases is likely to have applications in the biotechnology sector. Although our technology is most applicable for modeling simple dominant genetic diseases, it can be adapted to model recessive and complex disorders. Beyond increasing our understanding of human diseases, these cellular models represent useful screening tools for testing novel pharmacological treatments. Identification and development of these new therapies may support new companies or new products for existing companies. We hope that using stem cells to model neurodegenerative disorders will lead to progress in the fight against these diseases, as well as provide the tools and examples for those in academia and industry who hope to create stem cell models of other clinically important disorders.